

# Exhibit 58

Quingming Li

ZHP-288

4/16/2021

## RE: RE: Valsartan ESO GC Results- Unknown Peaks

**From:** "OMahony, Kevin" <kevin.omahony@novartis.com>  
**To:** "Quinn, Jannine" <jannine.quinn@novartis.com>, xavier <xavier@huahaipharm.com>  
**Cc:** tangyinhuia <tangyinhuia@huahaipharm.com>, chenyiyingzhi@huahaipharm.com, "Breen, Sarah" <sarah.breen@novartis.com>, "Hu, Brad" <brad.hu@novartis.com>, "Zhu, Bin-1" <bin-1.zhu@novartis.com>, 徐觅 <xumi@huahaipharm.com>, zhuling <zhuling@huahaipharm.com>, Minda Cai <cai@huahaipharm.com>, peng dong <dongpeng@huahaipharm.com>, xiongying <xiongying@huahaipharm.com>, minli <minli@huahaipharm.com>, jenson <jenson@huahaipharm.com>, "Lynch, Niamh" <niamh.lynch@novartis.com>  
**Date:** Tue, 05 Jun 2018 08:28:22 +0000  
**Attachments** REP-0909\_draft.docx (389.91 kB)

:

Dear Xavier,

We have done some testing in Solvias labs for Novartis of three batches of Huahai material and have a tentative assessment.

Please note in the Solvias testing Dichloromethane was not seen. I have asked the lab to confirm that this is definitely the case.

Can the Huahai colleagues please assess this and comment as soon as possible?

### Tentative identification of unknown peaks detected in Valsartan (Batch 18-038M01)

| Assigned pPeak (tentative) | VOC     | CA S No. | NI ST fit | RT (min) | RR T <sub>1</sub> | Comments  |
|----------------------------|---------|----------|-----------|----------|-------------------|---|
| 3                          | Propane | 74-98-6  | 76 7      | 2.0 6    | 0.2 9             | Likely a breakdown of a longer chain alkane on the GC |

| Assigned pPeak (tentative) | VOC                         | CA S No.      | NI ST fit | RT (min) | RR T <sub>11</sub> | Comments  |
|----------------------------|-----------------------------|---------------|-----------|----------|--------------------|---|
| 4                          | Butane                      | 106-97-8      | 95 3      | 2.5 1    | 0.3 5              | Likely a breakdown of a longer chain alkane on the GC |
| 7                          | Acetone                     | 67-64-1       | 99 9      | 4.2 1    | 0.5 8              | ICH class 3. 5000ppm limit.                           |
| 8                          | 2-Propanol                  | 67-63-0       | 97 0      | 4.3 9    | 0.6 1              | ICH class 3. 5000ppm limit.                           |
| 9                          | 2-methylpentane             | 107-83-5      | 89 6      | 4.9 0    | 0.6 8              | Isohexane so 290ppm can be assumed                    |
| 11                         | 2-methylpropanal            | 78-84-2       | 92 7      | 5.5 9    | 0.7 8              | Other name for Isobutyraldehyde. Also seen in Huahai  |
| 13                         | Butanal or 2-butanone       | e.g. 123-72-8 | 90 0      | 6.7 2    | 0.9 3              |   |
| 15                         | Isopropyl acetate           | 108-21-4      | 91 8      | 9.0 7    | 1.2 6              | Also seen in Huahai                                   |
| 16                         | Propanoic acid, ethyl ester | 105-37-3      | 91 8      | 11. 33   | 1.5 7              |   |
| 17                         | Propyl acetate              | 109-60-4      | 93 3      | 11. 57   | 1.6 1              | Also seen in Huahai                                   |
| 19                         | N-                          | 62-           | 99        | 15.      | 2.2                |   |

| Assigned pPeak (tentative) | VOC                               | CAS No.    | NIST fit | RT (min) | RR    | T <sub>121</sub> | Comments         |
|----------------------------|-----------------------------------|------------|----------|----------|-------|------------------|------------------|
|                            | Nitrosodimethyl amine (tentative) | 75-9       | 9        | 93       | 1     |                  | KOM 05 June 2018 |
| 20                         | Butyl acetate                     | 123-86-4   | 92 4     | 16. 90   | 2.3 5 |                  |                  |
| 21                         | Branched alkane                   | Grop up ID | 95 0     | 23. 27   | 3.2 3 |                  |                  |

Tentative identification of unknown peaks detected in Valsartan (Batch 18-042M01)

| Assigned peak (tentative) | VOC                             | CAS No.  | NIST fit | RT (min) | RR  | T <sub>121</sub> | Comments KOM 05 June 2018               |
|---------------------------|---------------------------------|----------|----------|----------|-----|------------------|---|
| 3                         | Propane                         | 74-98-6  | 90 8     | 2.07     | 0.2 | 9                |   |
| 4                         | Butane                          | 106-97-8 | 99 9     | 2.51     | 0.3 | 5                |   |
| 7                         | Acetone                         | 67-64-1  | 99 9     | 4.21     | 0.5 | 8                |   |
| 8                         | 2-Propanol                      | 67-63-0  | 98 0     | 4.39     | 0.6 | 1                |   |
| 9                         | 2-methylpentane                 | 107-83-5 | 92 9     | 4.90     | 0.6 | 8                |   |
| 10                        | 2-methyl-2-propanol (tentative) | 75-65-0  | 97 2     | 5.01     | 0.6 | 9                | Isomer of butanol which is ICH class 3. |

|    |                                    |               |      |        |       | 5000ppm limit              |
|----|------------------------------------|---------------|------|--------|-------|----------------------------|
| 12 | 2-methylpropanal                   | 78-84-2       | 99 4 | 5.60   | 0.7 8 |                            |
| 13 | Butanal or 2-butanone              | e.g. 123-72-8 | 91 2 | 6.72   | 0.9 3 |                            |
| 15 | Tetrahydrofuran                    | 109-99-9      | 97 3 | 7.61   | 1.0 5 | ICH Class 2. 720 ppm limit |
| 16 | Cyclohexane                        | 110-82-7      | 83 0 | 8.17   | 1.1 3 |                            |
| 17 | Isopropyl acetate                  | 108-21-4      | 91 9 | 9.07   | 1.2 6 |                            |
| 18 | Propanoic acid, ethyl ester        | 105-37-3      | 91 5 | 11.3 3 | 1.5 7 |                            |
| 19 | Propyl acetate                     | 109-60-4      | 93 5 | 11.5 7 | 1.6 0 |                            |
| 21 | N-Nitrosodimethylamine (tentative) | 62-75-9       | 99 9 | 15.9 3 | 2.2 1 |                            |
| 22 | Butyl acetate                      | 123-86-4      | 91 2 | 16.9 0 | 2.3 4 |                            |
| 24 | Branched alkane                    | Group ID      | 95 4 | 23.2 7 | 3.2 3 |                            |

Table 9: Tentative identification of unknowns detected in Valsartan (Batch 18-046M01)

| Assigned peak (tentative) | VOC     | CAS No.  | NIST fit | RT (min) | RRT <sup>13</sup> | Comments KOM 05 June 2018 |
|---------------------------|---------|----------|----------|----------|-------------------|---------------------------|
| 3                         | Propane | 74-98-6  | 843      | 2.06     | 0.29              |                           |
| 4                         | Butane  | 106-97-8 | 891      | 2.51     | 0.35              |                           |

|    |                                      |               |     |       |      |                                       |
|----|--------------------------------------|---------------|-----|-------|------|---------------------------------------|
| 7  | Acetone                              | 67-64-1       | 923 | 4.21  | 0.58 |                                       |
| 8  | 2-Propanol                           | 67-63-0       | 970 | 4.35  | 0.60 |                                       |
| 10 | 2-methylpentane                      | 107-83-5      | 886 | 4.90  | 0.68 |                                       |
| 12 | 2-methylpropanal                     | 78-84-2       | 999 | 5.60  | 0.78 |                                       |
| 13 | Butanal or 2-butanone                | e.g. 123-72-8 | 915 | 6.72  | 0.93 |                                       |
| 15 | Tetrahydrofuran                      | 109-99-9      | 859 | 7.61  | 1.06 |                                       |
| 16 | Formic acid, 1,1-dimethylethyl ester | 762-75-4      | 931 | 7.79  | 1.08 | Formic acid is class 3. 5000ppm limit |
| 17 | Isopropyl acetate                    | 108-21-4      | 898 | 9.07  | 1.26 |                                       |
| 18 | Propanoic acid, ethyl ester          | 105-37-3      | 897 | 11.33 | 1.57 |                                       |
| 19 | N-Nitrosodimethylamine (tentative)   | 62-75-9       | 969 | 15.92 | 2.21 |                                       |
| 20 | Butyl acetate                        | 123-86-4      | 881 | 16.91 | 2.35 |                                       |
| 21 | N,N-Dimethylacetamide                | 127-19-5      | 881 | 22.28 | 3.09 |                                       |
| 22 | Branched alkane                      | Group ID      | 957 | 23.27 | 3.23 |                                       |

Best regards,

**Kevin O'Mahony**  
AS&T Expert  
External Supply Operations (ESO)  
Novartis International  
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[kevin.omahony@novartis.com](mailto:kevin.omahony@novartis.com)  
[www.novartis.com](http://www.novartis.com)

---

**From:** Quinn, Jannine

**Sent:** 04 June 2018 23:26

**To:** xavier; OMahony, Kevin

**Cc:** tangyinhua; chenyingzhi@huahaipharm.com; Breen, Sarah; Hu, Brad; Zhu, Bin-1; 徐觅; zhuling; 'Minda Cai'; peng dong; xiongying; minli; jenson

**Subject:** RE: RE: Valsartan ESO GC Results- Unknown Peaks

Dear Xavier,

As a follow up to the DS Lot risk assessment can you advise if dichloromethane is a specified solvent in the starting material? Further to this, is it be possible to control the presence of dichloromethane in the starting material to ensure that the resulting DS lots consistently contain less than 60ppm of this solvent.

Further to this, it is noted that of the 8 samples DS lots which were quantified, 6 lots demonstrate a consistent level of dichloromethane (21-28ppm). The two remaining lots are higher at 62 and 78 ppm dichloromethane.

Can you comment on the following questions:-

- Did the 2 DS lots C5523-18-031M and C5523-18-033M used a specific lot of the starting material i.e. can we attribute a cause to the higher levels seen in these 2 lots?
- Is there evidence or a hypothesis to suggest that the typical level of dichloromethane should be in the range of 21 – 28ppm or is the range of 21 – 78ppm dichloromethane representative of the process?
- Do you propose to introduce a control for this material to ensure it is below 60ppm i.e. 10% of the ICH limit?

Thank you,

Jannine

**Jannine Quinn**

Project Team Leader [Launch and Transfer]

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M +353 87 2229249

[jannine.quinn@novartis.com](mailto:jannine.quinn@novartis.com)

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Ringaskiddy,  
County Cork  
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---

**From:** xavier [mailto:xavier@huahaipharm.com]

**Sent:** 04 June 2018 06:51

**To:** Quinn, Jannine; OMahony, Kevin

**Cc:** tangyinhua; chenyingzhi@huahaipharm.com; Breen, Sarah; Hu, Brad; Zhu, Bin-1; 徐觅; zhuling; 'Minda Cai'; peng dong; xiongying; minli; jenson

**Subject:** Re: RE: Valsartan ESO GC Results- Unknown Peaks

Dear Kevin, dear Jannine,

As promised, please kindly find the enclosed risk assessment for the additional batches as required.

Please kindly let us know if you have any further questions.

---

Best Regards

**HUAHAI PHARM**

**Mr. Xavier Tang 汤风扬**

Regional Representative, Sales & Marketing

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Tel: +86-576-85016411 Fax: +86-576-85991062

Mobile: +86-13706763070

Email: [xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)

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**From:** Quinn, Jannine

**Date:** 2018-06-01 15:05

**To:** xavier; OMahony, Kevin

**CC:** tangyinhua; chenyingzhi@huahaipharm.com; Breen, Sarah; Hu, Brad; Zhu, Bin-1; 徐觅; zhuling; Cai; peng dong; xiongying; minli; Jenson

**Subject:** RE: RE: Valsartan ESO GC Results- Unknown Peaks

Dear Xavier,

Thank you for your assistance with this.

Best regards,  
Jannine

**Jannine Quinn**  
Project Team Leader [Launch and Transfer]

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[jannine.quinn@novartis.com](mailto:jannine.quinn@novartis.com)

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---

**From:** xavier [mailto:[xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)]  
**Sent:** 01 June 2018 08:04  
**To:** Quinn, Jannine; OMahony, Kevin  
**Cc:** tangyinhua; chenyiingzhi@huahaipharm.com; Breen, Sarah; Hu, Brad; Zhu, Bin-1; 徐觅; zhuling; Cai; peng dong; xiongying; minli; Jenson  
**Subject:** Re: RE: Valsartan ESO GC Results- Unknown Peaks

Dear Jannie,

As agreed on today's TC, we will feedback with the risk assessment for the batches mentioned below by next Monday afternoon.

---

Best Regards

**HUAHAI PHARM**

**Mr. Xavier Tang 汤风扬**  
Regional Representative, Sales & Marketing

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Email: [xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)

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**From:** Quinn, Jannine  
**Date:** 2018-05-31 22:49  
**To:** xavier; OMahony, Kevin  
**CC:** tangyinhua; chenyingzhi@huahaipharm.com; Breen, Sarah; Hu, Brad; Zhu, Bin-1; Karen Xu; 朱玲; 'Minda Cai'; peng\_dong; xiongying; minli; jenson  
**Subject:** RE: Re: Valsartan ESO GC Results- Unknown Peaks

Dear Xavier,

Thanks to you and your team for providing the investigation report of the unknown peak in residual solvent of Valsartan in such a short timeframe to support the Novartis timeline for first Drug Substance release for Drug Product Validation.

Kevin is working through your report currently.

In the meanwhile, can you complete an evaluation of the lots already supplied to Novartis to confirm that the residual solvents peak responses for those individual batches are within the limits defined in the report.

Could you give your first attention to the lots listed below as these DS lots are to be used during next weeks for the first DP validations.

#18-028M01  
#18-029M01  
#18-030M01  
#18-031M01  
#18-033M01  
#18-009M01  
#18-010M01  
#18-011M01  
#18-012M01  
#18-013M01  
#18-019M01  
#18-020M01  
#18-014M01  
#18-027M01  
#18-032M01  
#18-034M01  
#18-035M01

Your assistance with this is much appreciated.

Thank you,  
Jannine

**Jannine Quinn**  
Project Team Leader [Launch and Transfer]

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[jannine.quinn@novartis.com](mailto:jannine.quinn@novartis.com)

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---

**From:** xavier [mailto:xavier@huahaipharm.com]  
**Sent:** 31 May 2018 13:38  
**To:** OMahony, Kevin  
**Cc:** tangyinhua; Quinn, Jannine; chenyingzhi@huahaipharm.com; Breen, Sarah; Hu, Brad; Zhu, Bin-1; Karen Xu; 朱玲; 'Minda Cai'; peng dong; xiongying; minli; jenson  
**Subject:** Re: Re: Valsartan ESO GC Results- Unknown Peaks

Dear Kevin,

Sorry to keep you waiting.

Please kindly find our investigation report of the unknown peak in residual solvent of Valsartan as attached.

Please also check the Chromatogram by Novartis method and the Identification of Dimethyl sulfide as required.

If you have any further queries, please feel free to let us know.

Thank you.

---

Best Regards

**HUAHAI PHARM**

**Mr. Xavier Tang 汤风扬**  
Regional Representative, Sales & Marketing

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Tel: +86-576-85016411 Fax: +86-576-85991062  
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Email: [xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)

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**From:** xavier  
**Date:** 2018-05-30 08:30  
**To:** OMahony, Kevin  
**CC:** tangyinhua; Quinn, Jannine; chenyingzhi@huahaipharm.com ; Breen, Sarah; Hu, Brad; Zhu, Bin-1; 徐觅; zhuling; Cai; peng dong; xiongying; minli; Jenson  
**Subject:** Re: RE: Valsartan ESO GC Results- Unknown Peaks  
Dear Kevin,

Sure, we will do our best.

---

Best Regards

**HUAHAI PHARM**

**Mr. Xavier Tang 汤风扬**  
Regional Representative, Sales & Marketing

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Email: [xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)

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**From:** OMahony, Kevin  
**Date:** 2018-05-29 17:57  
**To:** Huahaipharm  
**CC:** tangyinhua; Quinn, Jannine; chenyingzhi@huahaipharm.com ; Breen, Sarah; Hu, Brad; Zhu, Bin-1; 徐觅; 朱玲; Cai; peng dong; xiongying; minli; jenson  
**Subject:** RE: Valsartan ESO GC Results- Unknown Peaks  
Hi Xavier,

Would it be possible to share the initial data by Thursday 31<sup>st</sup> as  
we are looking to release by 31<sup>st</sup> June?

Best regards,

**Kevin O'Mahony**  
AS&T Expert  
External Supply Operations (ESO)  
Novartis International  
Pharmaceutical Ltd., Branch Ireland  
IE- Ringaskiddy, County Cork  
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[kevin.omahony@novartis.com](mailto:kevin.omahony@novartis.com)  
[www.novartis.com](http://www.novartis.com)

---

**From:** Huahaipharm [mailto:[xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)]

**Sent:** 29 May 2018 10:55

**To:** OMahony, Kevin

**Cc:** tangyinhua; Quinn, Jannine; chenyingzhi@huahaipharm.com; Breen, Sarah; Hu, Brad; Zhu, Bin-1; 徐冕; 朱玲; Cai; peng dong; xiongying; minli; jenson

**Subject:** Re: Valsartan ESO GC Results- Unknown Peaks

Hi Kevin,

Yes, studying work is on-going.

We will try the best to provide report including all info. you required on 1st June.

sent from my iPhone

在 2018年5月29日, 17:40, OMahony, Kevin

<[kevin.omahony@novartis.com](mailto:kevin.omahony@novartis.com)> 写道:

Dear Xavier,

Is there an update on how the identification work is going at Huahai?

Best regards,

**Kevin O'Mahony**  
AS&T Expert  
External Supply Operations (ESO)  
Novartis International  
Pharmaceutical Ltd., Branch Ireland  
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---

**From:** xavier [mailto:[xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)]

Sent: 25 May 2018 09:44

To: OMahony, Kevin; tangyinhua; Quinn, Jannine;  
[chenyingzhi@huahaipharm.com](mailto:chenyingzhi@huahaipharm.com); Breen, Sarah

Cc: Hu, Brad; Zhu, Bin-1; 徐觅; 朱玲; Cai; peng dong;  
xiongying; minli; jenson

Subject: Re: RE: Valsartan ESO GC Results- Unknown  
Peaks

Dear Kevin and Brad,

It was our great pleasure to have the TC with you today.

As agreed, we will try best to provide the report  
including the information as required by 31st May.

---

Best Regards

**HUAHAI PHARM**

**Mr. Xavier Tang** 汤风扬

Regional Representative, Sales & Marketing

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发件人: OMahony, Kevin  
发送时间: 2018-05-24 17:43  
收件人: xavier; tangyinhua; Quinn, Jannine;  
[chenyingzhi@huahaipharm.com](mailto:chenyingzhi@huahaipharm.com); Breen, Sarah  
抄送: Hu, Brad; Zhu, Bin-1; 徐觅; 朱玲; Cai; peng  
dong; xiongying  
主题: RE: RE: Valsartan ESO GC Results- Unknown  
Peaks

Thanks Xavier for you and your colleagues support with this.

- We actually use NMP as solvent so I am not certain that the larger peak after ethanol in our chromatogram is dimethyl sulphide. Have you some data to support your assessment of this peak by spiking or GC-MS etc.?

HH: Yes, please kindly find the chromatogram of GC-MS & Identification as attached.

[KOM 24 May 2018]: Thank you. As this peak is an interaction between DMSO and Valsartan this is not likely one of the peaks we are seeing in Novartis.

- Hexane and Dichloromethane are part of the Huahai validation but are not specified impurities in your method or the Novartis one so we have to consider how we deal with residual levels of these solvents in testing of the API to ensure that they are correctly identified and can be proven in each sample to be less than the ICH limits.

HH: Hexane and Dichloromethane are not intentionally added in our manufacturing process (Dichloromethane is introduced from the SM 4' - Bromomethyl-2' -cyano-1, 1' -biphenyl). After reviewing the historical data from Valsartan batches, the content of Dichloromethane is within the range of 14-77ppm, the content of Hexane is below 1ppm, both residues are far below ICH limit. (ICH limit: Dichloromethane 600ppm; Hexane 290ppm)

[KOM 24 May 2018]: Would it be possible to assess what level we are seeing in the Huahai batches listed in the word document. I appreciate you cannot necessarily re-analyse the batches but it would be good to have an idea of what level we are seeing now.

Maybe this would be possible by running a solution of hexane and DCM at low levels on the same GC as an indication of response? Or else if you are doing further GC-MS testing you may be able to properly identify/quantify them.

- For the Ethyl-propionate and n-propyl acetate proposed have you a proposed source?  
HH: Introduced from solvent ethyl acetate.  
[KOM 24 May 2018]: What specifications would be appropriate for these?

- Have you any possibility of performing identification work on the unidentified peaks?  
HH: We are proceeding the investigation on the unidentified peaks. We will keep you closely updated.  
[KOM 24 May 2018]: Thank you very much

I think that it may be a good ideal to have a call tomorrow to discuss the progress and action plans. I will set up a call.

Best regards,

**Kevin O'Mahony**  
AS&T Expert  
External Supply Operations (ESO)  
Novartis International  
Pharmaceutical Ltd., Branch Ireland  
IE- Ringaskiddy, County Cork  
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[www.novartis.com](http://www.novartis.com)

---

**From:** xavier  
[mailto:[xavier@huahaipharm.com](mailto:xavier@huahaipharm.com)]  
**Sent:** 24 May 2018 10:18  
**To:** OMahony, Kevin; tangyinhua; Quinn, Jannine; [chenyingzhi@huahaipharm.com](mailto:chenyingzhi@huahaipharm.com); Breen, Sarah  
**Cc:** Carmody, Corinna; Donnellan, Keith; Kearney, David; Doherty, Barry; Hu, Brad; Zhu, Bin-1; Higgins, Susan; 徐觅; 朱玲; Cai; peng dong; xiongying  
**Subject:** Re: RE: Valsartan ESO GC Results- Unknown Peaks

Dear Kevin,

Please kindly find the feedback from our QC as below:

We actually use NMP as solvent so I am not certain that the larger peak after ethanol in our chromatogram is dimethyl sulphide. Have you some data to support your assessment of this peak by spiking or GC-MS etc.?

HH: Yes, please kindly find the chromatogram of GC-MS & Identification as attached.

Hexane and Dichloromethane are part of the Huahai validation but are not specified impurities in your method or the Novartis one so we have to consider how we deal with residual levels of these solvents in testing of the API to ensure that they are correctly identified and can be proven in each sample to be less than the ICH limits.

HH: Hexane and Dichloromethane are not intentionally added in our manufacturing process ( Dichloromethane is introduced from the SM 4' - Bromomethyl-2' -cyano-1, 1' -biphenyl ). After reviewing the historical data from Valsartan batches, the content of Dichloromethane is within the range of 14-77ppm, the content of Hexane is below 1ppm, both residues are far below ICH limit. ( ICH limit: Dichloromethane 600ppm; Hexane 290ppm)

For the Ethyl-propionate and n-propyl acetate proposed have you a proposed source?

HH: Introduced from solvent ethyl acetate.

Have you any possibility of performing identification work on the unidentified peaks?

HH: We are proceeding the investigation on the unidentified peaks. We will keep you closely updated.

Please kindly let us know if you have any further query.

---

Best Regards

**HUAHAI PHARM**

Mr. Xavier Tang 汤风扬

Regional Representative, Sales &  
Marketing

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85991062

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**From:** OMahony, Kevin  
**Date:** 2018-05-23 17:43  
**To:** xavier; tangyinhua; Quinn, Jannine; chenyingzhi@huahaipharm.com; Breen, Sarah  
**CC:** Carmody, Corinna; Donnellan, Keith; Kearney, David; Doherty, Barry; Hu, Brad; Zhu, Bin-1; Higgins, Susan; Karen Xu; 朱玲; Cai  
**Subject:** RE: RE: Valsartan ESO GC Results- Unknown Peaks

Dear Xavier,

Thank you for the feedback.

We actually use NMP as solvent so I am not certain that the larger peak after ethanol in our chromatogram is dimethyl sulphide. Have you some data to support your assessment of this peak by spiking or GC-MS etc.?

Hexane and Dichloromethane are part of the Huahai validation but are not specified impurities in your method or the Novartis one so we have to consider how we deal with residual levels of these solvents in testing of the API to ensure that they are correctly identified and can be proven in each sample to be less than the ICH limits.

For the Ethyl-propionate and n-propyl acetate proposed have you a proposed source?

Have you any possibility of performing identification work on the unidentified peaks?

Best regards,

**Kevin O'Mahony**  
AS&T Expert  
External Supply Operations (ESO)  
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---

**From:** xavier  
[<mailto:xavier@huahaipharm.com>]

**Sent:** 23 May 2018 09:55

**To:** OMahony, Kevin; tangyinhua;  
Quinn, Jannine;  
[chenyingzhi@huahaipharm.com](mailto:chenyingzhi@huahaipharm.com);  
Breen, Sarah  
**Cc:** Carmody, Corinna; Donnellan,  
Keith; Kearney, David; Doherty, Barry;  
Hu, Brad; Zhu, Bin-1; Higgins, Susan;  
Karen Xu; 朱玲; Cai

**Subject:** Re: RE: Valsartan ESO GC  
Results- Unknown Peaks

Dear Kevin,

Please kindly find the feedback from our QC as below.

We have marked the peaks with our comments on the chromatogram.

<image001.jpg>

\*Dimethyl sulfide: Introduced from the reaction between Valsartan and DMSO

which is the diluent of residual solvent method

\*\*Unspecified peak 3: Introduced from the reaction between Valsartan and DMSO which is the diluent of residual solvent method

Please kindly let us know if you have any further queries.

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Best Regards

**HUAHAI PHARM**

**Mr. Xavier Tang 汤风扬**

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**From:** OMahony, Kevin  
**Date:** 2018-05-22 17:04  
**To:** [xavier](mailto:xavier); [tangyinhua](mailto:tangyinhua); [Quinn, Jannine](mailto:Quinn, Jannine); [chenyingzhi@huahaipharm.com](mailto:chenyingzhi@huahaipharm.com); Breen, Sarah  
**CC:** Carmody, Corinna; Donnellan, Keith; Kearney, David; Doherty, Barry; Hu, Brad; Zhu, Bin-1; Higgins, Susan  
**Subject:** RE: FW: Valsartan ESO GC Results- Unknown Peaks  
Thank you very much Xavier for providing he chromatograms.

It is good to see that we are seeing some extra peaks in Huahai chromatograms and that we are aligned in this.

Is there any information on what these extra peaks are? In particular the one after ethanol?

Also would it be possible to get the chromatograms from the second method at Huahai that is used for MTBE and DMF?

We will be providing our chromatograms today also.

<image002.png>

Best regards,

**Kevin O'Mahony**  
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**From:** xavier  
[<mailto:xavier@huahaipharm.com>]  
**Sent:** 22 May 2018 04:27  
**To:** OMahony, Kevin;  
tangyinhua; Quinn, Jannine;  
[chenyingzhi@huahaipharm.com](mailto:chenyingzhi@huahaipharm.com); Breen, Sarah  
**Cc:** Carmody, Corinna;  
Donnellan, Keith; Kearney,

David; Doherty, Barry; Hu,  
Brad; Zhu, Bin-1

**Subject:** Re: FW: Valsartan  
ESO GC Results- Unknown  
Peaks

Dear Kevin,

Our QC will check and  
comment soon.

Meanwhile, could you please  
kindly provide the  
chromatograms including  
peak areas for all related  
batches?

Thanks a lot.

---

Best Regards

**HUAHAI PHARM**

**Mr. Xavier Tang 汤风扬**  
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Sales & Marketing

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**From: OMahony, Kevin**

**Date:** 2018-05-22 00:00  
**To:** [tangyinhua](#); [xavier](#); Quinn, Jannine; [chenyingzhi@huahaipharm.com](#); Breen, Sarah  
**CC:** Carmody, Corinna; Donnellan, Keith; Kearney, David; Doherty, Barry; Hu, Brad; Zhu, Bin-1  
**Subject:** FW: Valsartan ESO GC Results- Unknown Peaks

Dear Huahai colleagues,

During our analysis of residual solvents by GC (using a combined method) at Novartis we have found a number of solvents that we cannot identify for the following batches.

The peak areas vary depending on the batch. These are the batches analysed.

| <u>Batch Number:</u> |            |
|----------------------|------------|
| #18-014M01           | #18-039M01 |
| #18-027M01           | #18-040M01 |
| #18-032M01           | #18-041M01 |
| #18-034M01           | #18-042M01 |
| #18-035M01           | #18-043M01 |
| #18-036M01           | #18-044M01 |

|            |            |
|------------|------------|
| #18-037M01 | #18-045M01 |
| #18-038M01 | #18-046M01 |

Please see these highlighted and zoomed in on Figure 1 and compared to solvent and reporting limit reference solution in figure 2.

We do use a different method but would expect you to have these peaks also if product related. I have attached the GC method for your convenience.

I would appreciate your support on this and feel free to call me if any further information is required.

**Figure 1:  
Zoomed in  
chromatogram  
of a Huahai  
batch #18-  
038M01**



**Figure 2:**  
Zoomed out  
chromatogram  
of a Huahai  
batch #18-  
038M01  
compared to a  
solvent and  
reference  
solution  
2.



Best regards,

**Kevin O'Mahony**  
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---

**From:** Kearney,  
David

Sent: 21 May 2018  
15:18  
To: OMahony, Kevin  
Cc: Breen, Sarah;  
Donnellan, Keith;  
Carmody, Corinna;  
Higgins, Susan  
Subject: Valsartan  
ESO GC Results-  
Unknown Peaks

Hi Kevin,

We have noted a number of unknown peaks in the chromatography for the Valsartan samples we are testing for ESO. Below is a screenshot of a sample in the current sequence with the 3 largest unknown peaks highlighted. I've included a solvent and RS2 chromatogram for comparison. The chromatography is typical across all Valsartan ESO samples tested so far however there is a significant variation, throughout the samples, in the peak area for the unknown peak at RT 2.7 in particular

<image003.png>

<image005.png>

We will be proceeding with an AQWA investigation to investigate these unknown peaks.

Just note that the raw data is still in the review process therefore the investigation will only be initiated once the raw data has been fully secondary reviewed.

Any questions let me know,

Thanking You and  
Kind Regards,  
David

**David Kearney**  
QC Analyst, High  
Volume 1 Testing unit,

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<sup>11</sup> Relative to ethyl acetate, see section 2.4 for calculation.

<sup>21</sup> Relative to ethyl acetate, see section 2.4 for calculation.

<sup>22</sup> Relative to ethyl acetate, see section 2.4 for calculation.